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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,171	11/18/2003	Brent R. Constantz	SKEL-008	5987

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EXAMINER
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ARNOLD, ERNST V

ART UNIT	PAPER NUMBER
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1616

DATE MAILED: 07/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/717,171	CONSTANTZ ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Ernst V. Arnold	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-29 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-29 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some    \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____.  |

### **DETAILED ACTION**

Applicant's arguments, see remarks, filed 03/08/2006, with respect to the rejection(s) of claim(s) 1-29 under 35 USC 103(a) have been fully considered and are persuasive. Therefore, the rejections have been withdrawn. Applicant has filed a terminal disclaimer to overcome the double patenting rejection, which is now withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of an alternative interpretation of Chow et al. (US 5,525,148). This action is non-final. Claims 1-29 are pending.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 9, and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 6, 9 and 19 recite "mimetic". The specification does not define mimetic in such a way so that one of ordinary skill in the art would recognize a mimetic. The description provided on page 9, lines 12-26 of the instant specification states that the compounds of interest include numerous chemical classes but fails to accurately describe a single mimetic (Page 9, line 14).

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 9 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear to the Examiner the metes and bounds of the term "mimetic". It is unclear if this is a structural mimetic or a functional mimetic.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 8 recites "binding fragment". It is unclear to the Examiner the metes and bounds of a fragment that can bind RANK and maintain function. The specification on pages 8-9 describes various fragments but does not provide guidance to one of ordinary skill in the art which fragment would function in the invention.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chow et al. (US 5,525,148) in view of Koide et al. (Biochem Biophys Res Commun 1999, 259, 97-102) and Constantz (US 6,375,935) and King et al. (US PG PUB 2004/0002770 filed on 06/02/2003) and Chow et al. (J. Biomed. Mater. Res. (Appl Biomater) 2000, 53, 511-517) and Constantz (US 6,375,935).

Applicant claims a method of producing a flowable composition that sets into a calcium phosphate containing product, said method comprising:

combining:

- (a) a setting fluid;
  - (b) dry reactants comprising a calcium source and a phosphate source; and
  - (c) an osteoclastogenic agent;
- in a ratio sufficient to produce said flowable material.

**Determination of the scope and content of the prior art**  
**(MPEP 2141.01)**

Chow et al. disclose the preparation of calcium phosphate cements by combining a first component comprising a calcium source and a phosphate source (as a powder; hence dry) and a second component comprising an aqueous setting fluid (Column 8, lines 4-15). The resulting composition can be readily modeled to accurately reconstruct bony cavities and missing bone and can be molded and sculpted or even supplied as a putty (Column 4, lines 30-38 and column 11, lines 3-7). The Examiner interprets that the ease of manipulation of the composition of Chow et al. to read on a flowable composition. Chow et al. disclose that various additives can be included into the composition including bone morphogenic proteins (Column 11, lines 51-59 and claim 26). Mixing of the ingredients produces a paste that sets into calcium phosphate containing product (Column 4, lines 39-45). Chow et al. disclose mixing 0.075 mL of aqueous solution with 0.3 grams of calcium phosphate cement powder, which is a ratio of 0.25:1 (Instant claim 10). Chow et al. disclose cements, slurries and pastes (Abstract; column 1, lines 12-17; column 4, lines 34-38 and column 11, lines 51-52) (Instant claim 11). Chow et al. disclose setting times between about 5 and 10 minutes with specific examples setting in 5, 7 and 8 minutes (See: Column 8, Table II, examples 1-4 and Column 9, Table II example 8 as representative examples) (Instant claims 13 and 21). Chow et al. disclose that the inventive cement can be employed to substitute for missing or defective bone or tooth tissue (hard tissue defects) and can be applied to the site of the defect with a spatula (column 4, lines 34-38 and column 11, lines 18-20) (Instant

Art Unit: 1616

claim 24). Chow et al. disclose kits of the composition (column 11, lines 12-15) (Instant claim 25).

Koide et al. teach that bone morphogenic protein-2 appears to be one of the regulating factors of osteoclastogenesis (Abstract). The Examiner interprets this to mean that the art recognizes bone morphogenic protein-2 to be an osteoclastogenic agent.

Constantz discloses methods and compositions where a soluble silicate solution is used as a setting fluid for calcium phosphate cements (Abstract; Column 7, Examples 1-3; and claim 1).

King et al. teach polymer-bioceramic structures for use in the repair of bone defects (Abstract). King et al. teach the ceramic matrix can consist of hydroxyapatite, beta-tricalcium phosphate, calcium sulfate and calcium carbonate (Claims 13). King et al. disclose the addition of a drug in the bioresorbable implantable bone repair structure wherein the drug comprises an osteogenic agent and bone morphogenic proteins (Claims 1, 17, and 21-24). King et al. disclose osteoprotegerin ligand (OPGL) as an osteogenic agent. The instant specification defines RANKL as also known as osteoprotegrin ligand (OPGL) (instant spec page 7, lines 26-30).

Chow et al. teach the measurement of both the diametral tensile strength and compressive strength of calcium phosphate cements under a variety of conditions (entire disclosure). The compressive strengths listed in the Chow et al. disclosure are within the range of the instant limitation. Chow et al. note that strengths of the cements

Art Unit: 1616

are expected to vary with the conditions under which the cement is used (Page 516, last paragraph).

Constantz discloses methods and compositions where a soluble silicate solution is used as a setting fluid for calcium phosphate cements (Abstract; Column 7, Examples 1-3; and claim 1).

**Ascertainment of the difference between the prior art and the claims  
(MPEP 2141.02)**

1. Chow et al. do not expressly teach the addition of an osteoclastogenic agent to the bone cement.

2. Chow et al. do not expressly disclose whether to mix the osteoinductive factor into the dry cement powder or the aqueous setting fluid (instant claims 2, 3, 16 and 17).

3. Chow et al. do not expressly disclose the solution of a soluble silicate as the setting fluid in their methods for making calcium phosphate containing cements.

4. Chow et al. do not expressly disclose methods of producing a flowable composition comprising an osteoclastogenic agent, which comprises a modulator (ligand) of RANK mediated osteoclastogenesis.

5. Chow et al. disclose the measurement of the diametral tensile strength of their calcium phosphate containing cements but do not expressly disclose measurement of the compressive strength (Column 8, lines 12-21 and column 9, Table II).

6. Chow et al. do not expressly disclose adding a soluble silicate to the composition as described above.



**Finding of prima facie obviousness**

**Rational and Motivation (MPEP 2142-2143)**

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to add bone morphogenic protein 2, an osteoclastogenic agent as reported by Koide et al., to the bone cement of Chow et al. and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Chow et al. suggest adding bone morphogenic proteins to the bone cement. Thus, the disclosure of Chow et al. intrinsically includes both means to recruit osteoblasts (osteoinductive factor) and means to lead to the production of osteoclasts (bone morphogenic protein). Koide et al. further state that bone morphogenic proteins are finding use in orthopedics, dentistry, periodontology and plastic surgery (Page 101, last paragraph).

2. It is prima facie obvious to one of ordinary skill in the art to mix the osteoinductive factor into one or the either or both. See: In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results); In re Gibson, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is prima facie obvious.)

3. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the calcium phosphate cement of Chow et al. by using a soluble silicate as suggested by Constantz and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Constantz disclose that the calcium phosphate cements employing silicate liquids may be mixed very quickly and easily without specialized mixing devices, set rapidly, and are able to obtain higher strengths due to the lower liquids to solids ratios employed (Column 7, lines 54-60).

4. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the composition of Chow et al. with a ligand for RANK for the purpose of modulating osteoclast cells to produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Chow et al. suggest that bone growth regulating agents, i.e., bone morphogenic proteins which are art recognized osteoclastogenic agents, can be incorporated into the composition which would aid in the healing process. The teaching by Chow et al. of adding an osteoclastogenic agent to the bone cement renders other osteoclastogenic agents obvious to one of ordinary skill in the art. The teaching of King et al. teaches OPGL as suitable for use in calcium phosphate containing products. The adjustment of particular working conditions (i.e., the choice of RANK ligand: mimetic, polypeptide, binding fragment, small molecule, etc...) is deemed merely a matter of judicious selection and routine optimization of standard working conditions, which is well within the purview of one of ordinary skill in the art.

5. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to measure the compressive strength of the calcium phosphate containing composition of Chow et al.

Since the composition of Chow et al. (US 5,525,148) appears to be same as the claimed invention then it would intrinsically have a compressive strength within the instantly claimed limitations because a composition and it's properties are inseparable. In addition, the Office is not equipped with the scientific equipment to test the composition of Chow et al. for it's compressive strength. So, when the compositions appear to be the same and the Examiner cannot determine ascertain a specific physical property of the composition in question then the burden appropriately falls upon the Applicant to demonstrate the difference.

6. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the calcium phosphate cement kit of Chow et al. by using a soluble silicate as suggested by Constantz and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Constantz disclose that the calcium phosphate cements employing silicate liquids may be mixed very quickly and easily without specialized mixing devices, set rapidly, and are able to obtain higher strengths due to the lower liquids to solids ratios employed (Column 7, lines 54-60).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

***Conclusion***

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

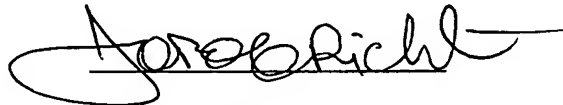
No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (6:15 am-3:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ernst Arnold  
Patent Examiner  
Technology Center 1600  
Art Unit 1616  
May 02, 2006

A handwritten signature in black ink, appearing to read "Johann Richter", with a large, stylized flourish extending from the end of the name.

Johann Richter, Ph.D. Esq.  
Supervisory Patent Examiner  
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